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[C2H2305] Inclisiran (Leqvio)

1. Purpose of use

Patients with familial hypercholesterolemia (FH) or hypercholesterolemia (non-FH) who are at high risk of cardiovascular disease, and for whom a maximally tolerated dose of HMG-CoA reductase inhibitors has been insufficient or who are intolerant to these inhibitors.

2. Price of the drug

Inclisiran has been reimbursed since November 2023, and its drug price is JPY 443,548 as of April 2025. The price is determined based on the Similar Efficacy Comparison Method (I) with a usefulness premium (I) of 40%. The product is designated as an item for cost-effectiveness evaluation with H1 classification.

3. Scope of Cost-effectiveness Evaluation

This product is used to lower LDL cholesterol (LDL-C) levels in patients with FH or non-FH. The scope of evaluation agreed upon at the first session of the Expert Committee of Cost-Effectiveness Evaluation (ECCEE) is described below:

Target population	(a) Non-FH patients with a history of atherosclerotic cardiovascular disease (ASCVD) for whom treatments with evolocumab self-administration are difficult for inevitable reasons such as limited physical or cognitive functions (b) Non-FH patients with a history of atherosclerotic cardiovascular disease who are not categorized as the population (a) (c) FH patients with a history of ASCVD (d) FH patients without a history of ASCVD
Comparator	(a) Standard of care (SoC)

	(b)(c)(d) Evolocumab

4. Evaluation of additional benefits

Population (a): Non-FH patients with a history of ASCVD for whom treatments with evolocumab self-administration are difficult for inevitable reasons

The academic group performed a meta-analysis of five randomized controlled trials (RCTs) (ORION-1, 10, 11, 15, 18) comparing inclisiran and placebo. The result showed that the between-group difference in LDL-C change rate [95% CrI] was -53.11% [-54.62, -51.59] in the fixed-effect model and -56.01% [-64.61, -47.41] in the random-effect model. Since inclisiran statistically significantly reduced LDL-C levels compared to placebo, the academic group evaluated that it had an additional benefit over SoC.

Population (b): Non-FH patients not categorized as population (a)

In the academic analysis, owing to high heterogeneity between the identified trials of inclisiran and evolocumab, an indirect comparison was not conducted. Instead, meta-analyses comparing inclisiran and placebo using five trials and evolocumab and placebo using seven trials were performed. The results showed that the between-group difference in LDL-C change rate [95% CrI] for inclisiran versus placebo was -53.11% [-54.62, -51.59] in the fixed-effect model and -56.01% [-64.61, -47.41] in the random-effect model. For evolocumab versus placebo, the between-group difference [95% CrI] was -62.05% [-62.91, -61.18] in the fixed-effect model and -68.53% [-71.71, -65.34] in the random-effect model. While clearly interpreting the superiority of the efficacy of the two drugs is difficult, the results do not indicate that inclisiran significantly reduces LDL-C more than evolocumab. Therefore, the academic analysis evaluated that inclisiran had not shown an additional benefit over evolocumab.

Population (c)(d): FH patients

According to the manufacturer’s analysis, populations (c) and (d) were evaluated as a whole, since the results of subgroup analysis for FH by a history of ASCVD events were not reported in all trials identified in the systematic review. As with the abovementioned population (b), comparisons were conducted between inclisiran and placebo, and evolocumab and placebo, respectively.

The meta-analysis of two trials showed that the between-group difference in LDL-C change rate [95% CrI] for inclisiran versus placebo was -45.59% [-49.55, -

41.62] in the fixed-effect model and -48.76% [-120.95, 23.44] in the random-effect model. For evolocumab, only one trial was available, and the between-group difference in LDL-C change rate in that trial was -59.2% [-65.1, -53.4]. While clearly interpreting the superiority of the efficacy of the two drugs is difficult, the results do not indicate that inclisiran significantly reduces LDL-C more than evolocumab. Therefore, the academic analysis evaluated that inclisiran had not shown an additional benefit over evolocumab.

5. Results of the cost-effectiveness analysis

The cost-effectiveness analysis conducted by the manufacturer for populations (a)–(d) was based on the changes in LDL-C observed in the series of ORION trials. Using a Markov model, the analysis predicted reduction in cardiovascular event risks, estimating the extent of reduction in cardiovascular-related deaths, direct medical costs, and utility improvements, based on risk reduction. The academic group revised the parameters of direct medical costs after cardiovascular events and the efficacy parameter for inclisiran for population (a). For populations (b)–(d), cost-minimization analyses were conducted as the academic group evaluated that inclisiran had not shown an additional benefit for the population groups.

The results are shown below.

Population	Comparator	ICER (JPY/QALY)
(a) Non-FH patients with a history of ASCVD for whom treatments with evolocumab are difficult for inevitable reasons	SoC	7,212,577
(b) Non-FH patients with a history of ASCVD not categorized as population (a)	Evolocumab	Cost increase
(c) FH patients with a history of ASCVD	Evolocumab	Cost increase
(d) FH patients without a history of ASCVD	Evolocumab	Cost increase